CLAIMS

We claim:

1. A method for inducing a biological response in a biological system comprising one or more receptors which comprises the step of introducing into the biological system a multivalent ligand which comprises a plurality of signal recognition elements recognized by at least one of the receptors and bonded to a molecular scaffold.

2. The method of claim 1 wherein the biological system comprises a cell having one or more cell receptors to which at least one of the signal recognition elements bind.

3. The method of claim 2 wherein binding of the signal recognition element to the receptor induces an intracellular response and/or an intercellular response.

4. The method of claim 2 wherein the cell is a prokaryotic cell.

5. The method of claim 2 wherein the biological response is chemotaxis.

6. The method of claim 1 wherein the signal recognition element is a saccharide and the multivalent ligand comprises a plurality of the saccharides that function as chemoattractants covalently attached to a molecular scaffold.

7. The method of claim 2 wherein the biological response is the formation of a biofilm.

8. The method of claim 2 wherein the biological response is nutrient uptake.

9. The method of claim 2 wherein the cell is a eukaryotic cell.

10. The method of claim 1 wherein the multivalent ligand modulates signal transduction mediated by G-protein coupled receptors.

11. The method of claim 10 wherein signal transduction is mediated by receptors.

12. The method of claim 11 wherein the eukaryotic cell is an epithelial cell or an endothelial cell.

13. The method of claim 11 wherein the eukaryotic cell is a cell of the immune system.

14. The method of claim 11 wherein the eukaryotic cell is a lymphocyte or a leukocyte.

15. The mmethod of claim 11 wherein the eukaryotic cell is a hematopoietic cell.

16. The method of claim 11 wherein the eukaryotic cell is a stem cell.

17. The method of claim 11 wherein the eukaryotic cell is a liver cell, muscle cell, or neuronal cell.

18. The method of claim 11 wherein the eukaryotic cell is a neutrophil.

19. The method of claim 18 wherein the response is chemotaxis.

20. The method of claim 11 wherein the eukaryotic cell is a human cell.

21. The method of claim 11 wherein the biological response is an intracellular signal by the cell.

22. The method of claim 21 wherein the multivalent ligand initiates or enhances the release of the intracellular signal.

23. The method of claim 11 wherein the cell is a B-cell or a T-cell.

24. The method of claim 23 wherein the multivalent ligand comprises a signal recognition element that is an epitope foreign to the organism from which the B-cell or T-cell originates.

25. The method of claim 24 wherein the multivalent ligand further comprises a signal recognition element that binds to a cell surface receptor of a B-cell or a T-cell.

26. The method of claim 25 wherein the multivalent ligand functions to enhance immunogenicity of the foreign epitope.

27. The method of claim 25 wherein the multivalent ligand comprises a signal recognition element that is an epitope recognized as a self epitope by the B-cell or T-cell.

28. The method of claim 27 wherein the multivalent ligand further comprises one or more different signal recognition element that bind to one or more cell surface receptorsof a B-cell or a T-cell.

29. The method of claim 27 wherein the multivalent ligand functions to sensitize the cell to the self epitope.

30. The method of claim 29 wherein the multivalent ligand further comprises one or more different signal recognition elements that bind to one or more cell surface receptors of a B-cell or a T-cell.

31. The method of claim 29 wherein the epitope is an epitope that is characteristic of a cancer cell.

32. The method of claim 25 wherein the multivalent ligand comprises at least one signal recognition element that is a self epitope which is recognized as a foreign epitope by the B-cell or T-cell.

33. The method of claim 32 wherein the multivalent ligand further comprises one or more signal recognition elements that bind to one or more different cell surface receptors of a B-cell or a T-cell.

34. The method of claim 32 wherein the multivalent ligand functions to tolerize the cell to the self epitope that is recognized as a foreign epitope by the B-Cell or T-cell.

35. The method of claim 1 wherein the multivalent ligand reorganizes receptors on the surface of a cell to modulate the biological response.

36. The method of claim 35 wherein the relative positions of different receptors on the cell surface is changed to modulate the response.

37. The method of claim 35 wherein interactions between cell surface receptors are changed to modulate the response.

38. The method of claim 1 wherein the biological response is an immune response to an antigen or epitope that is foreign to the biological system.

39. The method of claim 38 wherein the multivalent ligand contains one or more signal recognition elements, wherein said elements are antigens or epitopes, and wherein said elements are the same or different.

40. The method of claim 1 wherein the biological system is an animal.

41. The method of claim 1 wherein the biological system is a mammal.

42. The method of claim 1 wherein the biological system is a human.

43. The method of claim 1 wherein the biological system is a cell sample from an animal.

44. The method of claim 43 wherein the animal is a human.

45. The method of claim 1 wherein the response is cell migration, cell adhesion, or the formation of cell to cell junctions.

46. The method of claim 45 wherein the multivalent ligand inhibits cell migration, cell adhesion, or the formation of cell to cell junctions.

47. The method of claim 46 wherein the cell is a cancer cell in an animal.

48. The method of claim 1 wherein the multivalent ligand further comprises one or more binding recognition elements, one or more functional elements or both.

49. The method of claim 48 wherein the binding recognition element is a metal-chelating group.

50. The method of claim 49 wherein the metal-chelating group is a nickel-chelating group.

51. The method of claim 48 wherein one or more of the binding recognition elements binds to a protein.

52. The method of claim 48 wherein one or more of the functional elements is a label or a reporter group.

53. The method of claim 1 wherein one or more of the signal recognition elements is selected from the group consisting of an amino acid, a peptide, a protein, a derivatized peptide, a monosaccharide, a disaccharide, a polysaccharide, a nucleic acid, a cell nutrient, an epitope, an antigenic determinant, a small drug-like compound, a hapten, an antibody or antibody fragment or a cell surface receptor.

54. The method of claim 1 wherein one or more of the signal recognition elements is selected from the group consisting of an antigen, or an epitope.

55. The method of claim 1 wherein the multivalent ligand comprises a defined number of signal recognition elements.

56. The method of claim 1 wherein the multivalent ligand comprises about 25 or more signal recognition elements .

57. The method of claim 1 wherein the multivalent ligand comprises about 100 or more signal recognition elements.

58. The method of claim 1 wherein the signal recognition elements are covalently bonded to the molecular scaffold.

59. The method of claim 1 wherein the signal recognition elements are noncovalently bonded to the molecular scaffold.

60. The method of claim 1 wherein the signal recognition elements of the multivalent ligands are formed by noncovalently bonding a signal to one or more binding recognition elements.

61. The method of claim 60 wherein the binding recognition elements are saccharides and the signals are peptides or proteins which bind noncovalently to the saccharides.

62. The method of claim 61 wherein the signals are lectins.

63. The method of claim 62 wherein the lectins are Concanavalin A.

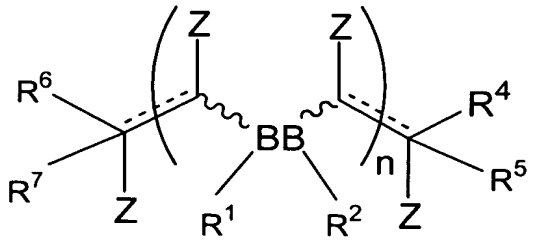
64. The method of claim 60 wherein the binding recognition elements are metal-chelating groups complexed to a metal and the signals are peptides or proteins which bind noncovalently to the metal.

65. The method of claim 1 wherein the molecular scaffold is selected from the group consisting of a polyacrylamide, a polyester, a polyether, a polymethacrylate, a polyol, and a polyamino acid.

66. The method of claim 1 wherein the molecular scaffold is a ROMP polymer.

67. The method of claim 1 wherein the molecular scaffold is an ATRP polymer.

68. The method of claim 1 wherein the multivalent ligand has the structure:



wherein:

n is an integer that is 2 or more which represents the number of repeating units within the parentheses in the ligand;

the dashed lines indicate optional double bonds;

"BB" represents the backbone repeating unit, which may be cyclic or acyclic, and may be the same or different in a random or block arrangement, the wavy lines indicating that a BB unit may be in either a cis or trans configuration in the ligand backbone;

each R^1 and R^2, independently of other R^1 and R^2 in the ligand, can be H or an organic group, a recognition element -L^2-BRE, a functional element -L^3-FE or a signal recognition element -L^1-SRE or both of R^1 and R^2 can be the -L^1-SRE group;

wherein L^{1-3}, independently, represent optional linker groups which may be the same or different in different repeating units;

R^4 and R^5 are H, or an organic group;

R^6 and R^7 are H, an organic group or an end-group; and

Z , independently of other Z in the ligand, is H, OH, OR^8, SH, a halide (F, Br, Cl, I), NH_2 or $N(R^8)_2$, where R^8 is H or an organic group or Z is absent when the optional double bond is present.

69. The method of claim 68 wherein SRE is a peptide or a derivatized peptide, a chemoattractant, a small drug-like compound, an antigen, an epitope, an antibody or antibody fragment

70. The method of claims 68 wherein at least one of SRE is an epitope or antigen and at least one other SRE binds to a cell surface receptor of an immune cell.

71. The method of claim 68 wherein at least one R^1 or R^2 is an -L^3-FE group which is a detectable label or a reporter group.

72. The method of claim 68 wherein at least one R^1 or R^2 is an -L^2-RE group.

73. The method of claim 68 wherein an FE in the at least one -L^2-FE group in the ligand is a detectable label or a reporter group.

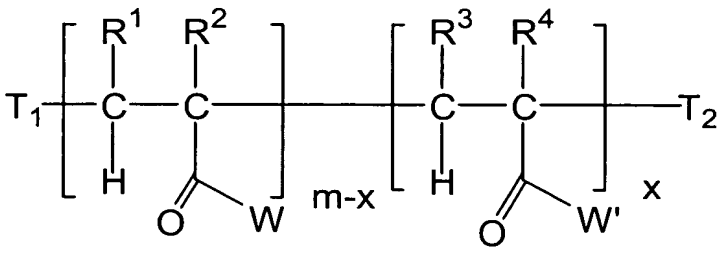
74. The method of claim 68 wherein an FE in the at least one -L^2-FE group in the ligand is an enzyme.

75. The method of claim 68 wherein the at least one BRE is a metal-chelating group.

76. The method of claim 68 wherein the at least one BRE is a nickel-chelating group.

77. The method of claim 68 wherein the at least one BRE is a metal-chelating group bound to a metal.

78. The method of claim 1 wherein the multivalent-ligand are polymers having the formula:



where:

m and x are integers and m is the number of monomers in the polymer;

W and W' are groups independently selected from –L-BRE, -L-FE, -L-SRE, a hydrogen or an organic group;

L is an optional linker group;

T_{1-2} are polymer end groups which can include, among others, reactive or non-reactive groups and latent reactive groups; and

R^{1-4} can be the same or different groups and are most generally, independently of one another, hydrogen or any organic groups and where

the polymeric ligand contains at least one W or W' that is a BRE or an SRE group.

79. The method of claim 78 wherein SRE is a peptide or a derivatized peptide, a chemoattractant, a small drug-like compound, an antigen, an epitope, an antibody or antibody fragment.

80. The method of claim 78 wherein SRE is an N-formyl peptide.

81. The method of claim 78 wherein SRE is a monosaccharide, disaccharide or trisaccharide.

82. The method of claims 78 wherein at least one of SRE is an epitope or antigen and at least one other SRE binds to a cell surface receptor of an immune cell.

83. The method of claim 78 wherein at least one FE group is a detectable label or a reporter group.

84. The method of claim 78 wherein an FE in the at least one $-L^2-FE$ group in the ligand is an enzyme.

85. The method of claim 78 wherein the at least one BRE is a metal-chelating group.

86. The method of claim 78 wherein the at least one BRE is a nickel-chelating group.

87. The method of claim 78 wherein the at least one BRE is a metal-chelating group bound to a metal.

88. The method of claim 78 wherein one or more of the BRE, SRE or both are Fab or Fab'.

89. A method for enhancing aggregation of biological particles which comprises the steps of:
providing a multivalent ligand complex which comprises a plurality of recognition elements which each induce aggregation of one or more of the biological particles and contacting the biological particles with the complex.

90. The method of claim 89 wherein the recognition elements are antibodies or lectins.

91. The method of claim 89 wherein the biological particles are cells, viruses or virions.

92. The method of claim 89 wherein the multivalent ligand is a ROMP-derived ligand.

93. The method of claim 89 wherein the multivalent ligand is an ATRP polymer.

94. The method of claim 89 wherein the multivalent ligand is bonded to a solid support.

95. A method for inducing or enhancing induction of a cellular response which comprises the steps of:
forming a multivalent ligand which comprises a plurality of signal recognition elements which indiviudally bind to the cell and induce the cellular response and
contacting the cells with the multivalent ligand in an amount sufficient to enhance the cellular response.

96. The method of claim 95 wherein the cellular response is intracellular release of a chemical species or a biological molecule.

97. The method of claim 95 wherein the cellular response is apoptosis.

98. The method of claim 95 wherein the cellular response is cell activation.

99. The method of claim 95 wherein one or more of the signal recognition elements are selected from lectins, proteins, nucleic acids, small drug-like compounds, antigens, epitopes, antibodies, antibody fragments, saccharides or mixtures thereof.

100. The method of claim 95 wherein the multivalent ligand is a ROMP-derived polymer or an ATRP polymer.

101. A method for generating an assembly of biological macromolecules or particles which comprises the steps of:

(a) providing a multivalent ligand which comprises a molecular scaffold to which a plurality of binding recognition elements are attached which, in turn, bind to one or more biological macromolecules or biological particles wherein the number, density and spacing of recognition elements bonded to the molecular scaffold are controlled; and

(b) contacting the multivalent ligand with biological macromolecules or particles such that the recognition elements of the ligand bind to two or more biological macromolecules or biological particles.

102. The method of claim 101 wherein the biological macromolecules are peptides or proteins.

103. The method of claim 101 wherein the biological particles are cells, viruses or virions.

104. The method of claim 101 wherein the multivalent ligand further comprises one or more FE bonded to the molecular scaffold.

105. The method of claim 101 wherein the FE is a group that can be attached to a solid support.

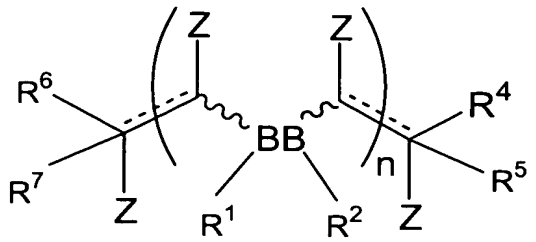
106. The method of claim 101 wherein the members of the assembly of biological macromolecules are attached to a solid support.

107. The method of claim 101 wherein the BRE are selected from saccharides, amino acids, peptides, or nucleic acids.

108. The method of claim 101 wherein the BRE are selected from antibodies, antibody fragments, anitgens, or epitopes.

109. The method of claim 101 wherein the molecular scaffold is a polymer.

110. A multivalent ligand having the structure:



wherein:

n is an integer that is 2 or more which represents the number of repeating units within the parentheses in the ligand;

the dashed lines indicate optional double bonds;

"BB" represents the backbone repeating unit, which may be cyclic or acyclic, and may be the same or different in a random or block arrangement, the wavy lines indicating that a BB unit may be in either a cis or trans configuration in the ligand backbone;

each R^1 and R^2, independently of other R^1 and R^2 in the ligand, can be H or an organic group, a recognition element -L^2-BRE, a functional element -L^3-FE or a signal recognition element -L^1-SRE or both of R^1 and R^2 can be the -L^1-SRE group;

wherein L^{1-3}, independently, represent optional linker groups which may be the same or different in different repeating units;

R^4 and R^5 are H, or an organic group;

R^6 and R^7 are H, an organic group or an end-group; and

Z, independently of other Z in the ligand, is H, OH, OR^8, SH, a halide (F, Br, Cl, I), NH2 or N(R^8)2, where R^8 is H or an organic group or Z is absent when the optional double bond is present.

111. The multivalent ligand of claim 110 wherein BRE, SRE or both are selected from the groups peptides, derivatized peptides, proteins, cell-surface receptors, saccharides, lectins, nucleic acids, antibodies, antibody fragments, antigens, epitopes, cells, viruses, and virions.

112. The multivalent ligand of claim 110 wherein FE are reporter groups or labels.

113. The multivalent ligand of claim 110 wherein BRE are metal-chelating groups or metal-chelating groups bonded to metals.

114. The multivalent ligand of claim 110 which comprises at least two different SRE.

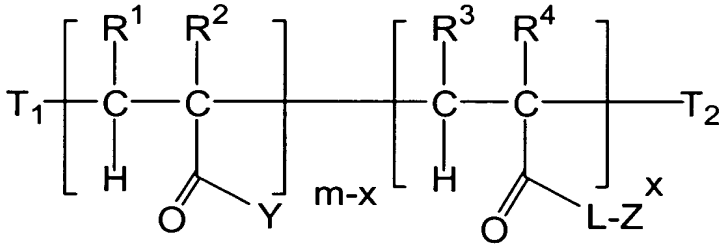
115. The multivalent ligand of claim 110 which comprises at least one BRE and at least one SRE.

116. The multivalent ligand of claim 110 wherein at least one SRE or BRE is a recognition molecule selected from the group consisting of Fab, Fab', scFv and scFv-hybrid.

117. The multivalent ligand of claim 116 which comprises at least two recognition molecules of different specificities..

118. A library of multivalent ligands of claim 110 in which the members of the libraries vary in the type, number and/or relative positioning of RE groups, combinations of BRE and SRE, the presence and/or positioning of spacers, in the number of repeating units or monomers and in the presence, type or number of FE.

119. A multivalent ligand having the formula:



where:

m and x are integers, x is the number of monomers carrying a Z group and m is the number of monomers in the polymer; the structure of the above formula reflects the relative number, but does not reflect the relative positions of Y and Z groups in the polymer;

Z is a metal chelating group or a metal chelating group chelated to one or more metal species;

Y is a chemical group that is not a metal chelating group, which more specifically can be selected from any organic group, an $-L^2$-BRE group, an $-L^3$-FE group, or an $-L^1$-SRE;

T_{1-2} are polymer end groups which can include, among others, reactive or non-reactive groups and latent reactive groups;

L and L^{1-3} are optional linker groups; and

R^{1-4} can be the same or different groups and are most generally, independently of one another, hydrogen or any organic groups, or more particularly hydrogen or any hydrocarbyl groups, as well as hydrocarbyl groups substituted with one or more

heteroatoms, one or more halogens, one or more -SR^5 groups, one or more -OR^5 groups, where R^5 is a hydrogen or any organic groups, including hydrocarbyl groups and substituted hydrocarbyl groups, one or more amine groups -$N(R^5)^2$ where R^5, independent of other R^5 groups is a hydrogen, or any organic groups again including any hydrocarbyl or substituted hydrocarbyl groups, or one or more halogen groups.

120. The multivalent ligand of claim 119 wherein BRE, SRE or both are selected from the groups peptides, derivatized peptides, proteins, cell-surface receptors, saccharides, lectins, nucleic acids, small drug-like compounds, antibodies, antibody fragments, antigens, epitopes, cells, viruses, and virions.

121. The multivalent ligand of claim 119 wherein FE are reporter groups or labels.

122. The multivalent ligand of claim 119 wherein BRE are metal-chelating groups or metal-chelating groups bonded to metals.

123. The multivalent ligand of claim 119 which comprises at least two different SRE.

124. The multivalent ligand of claim 119 which comprises at least one BRE and at least one SRE.

125. The multivalent ligand of claim 119 wherein at least one SRE or BRE is a recognition molecule selected from the group consisting of Fab, Fab', scFv and scFv-hybrid.

126. The multivalent ligand of claim 119 which comprises at least two recognition molecules of different specificities.

127. A library of multivalent ligands of claim 119 in which the members of the libraries vary in the type, number and/or relative positioning of RE groups, combinations of BRE and SRE, the presence and/or positioning of spacers, in the number of repeating units or monomers and in the presence, type or number of FE.